

**REMARKS**

Claims 1-17, 22-24, and 31-44 were pending. Claims 18-21 and 25-30 remain withdrawn by the Examiner as relating to a non-elected invention. Claims 1-3, 5, 8, 10, 11, 14, 23-24, 31-33, 36, 38-42, and 44 are amended herewith. Support for the amendments is found throughout the originally filed specification at, *e.g.*, page 6, lines 6-9, and page 57, lines 26-28. Claims 2, 4, 9, and 22 are canceled herein. New claims 45-50 are added. Support for these claims is found throughout the specification at, *e.g.*, page 3, lines 7-12. It is believed no new matter has been added. Claims 1-8, 10-17, 23-24, and 31-50 are currently pending.

**Formal Matters**

Applicants gratefully acknowledge the entry the Amendment filed on July 17, 2003, the grant of the benefit of the priority to the related provisional applications, the withdrawal of the outstanding objections to the specification and claim 10, and the withdrawal of certain rejections under 35 U.S.C. § 112, first and second paragraphs.

Applicants include herewith a copy of the Supplementary Information Disclosure Statement mentioned in the Amendment filed on July 17, 2003 and filed on August 4, 2003 for the convenience of the Examiner.

Applicants note that the Examiner has requested clarification regarding the identity of the host cell used to produce genes in Example 1. The host cell used in Example 1 of the specification is *E.coli*. The supplemental examples provided in the declaration used nitrilases produced in *Pseudomonas*.

**Objection to the Specification**

The Amendment filed July 17, 2003 is objected to under 35 U.S.C. § 132 because it allegedly introduces new matter into the disclosure. According to the Examiner, the added new material not supported by the original disclosure is the definition of enzyme preparations BD 1911 and BD 1921 as particular SEQ ID NOs. Applicants traverse this rejection.

Applicants respectfully submit that defining the enzyme preparations BD 1911 and BD 1921 as particular SEQ ID NOs is fully supported by the disclosure of the specification and therefore does not constitute new matter. Under 35 U.S.C. § 132, the “fundamental inquiry is whether the material added by amendment was inherently contained in the original application.” *Schering Corp. v. Amgen Inc.*, 55 U.S.P.Q.2d 1650, 1653 (Fed. Cir. 2000). The sequences of the enzymes BD 1911 and BD 1912 are expressly disclosed in the sequence listing of the originally filed application. These same sequences were used to produce the enzymes in the host cell as described and tested in Example 1. The sequences are also identified as nitrilases that can hydrolyze the transient amino nitrile or cyanohydrin under Strecker conditions. *See* the specification at page 6, lines 6-9. Therefore, the identity of these enzymes as the particular sequences is inherent in the disclosure of the specification as filed. Moreover, the addition of identifying information to the specification does not alter or expand the scope or teachings of the original disclosure. Thus, defining the enzyme preparations as the disclosed SEQ ID NOs fails to constitute new matter.

In view of the above, Applicants respectfully submit that the objection is overcome and request that it be withdrawn.

**Rejections Under 35 U.S.C. § 112, second paragraph**

Claims 2-10 remain rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite for the meaning of “\*” by the center “C”. Claims 22-24 remain rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite for the phrases “amino acid as set forth in SEQ ID NO: 2 or SEQ ID NO:4” and “a nucleic acid sequence as set forth in SEQ ID NO:1 or SEQ ID NO:3” and claims 38-42 and 44 are added to this rejection. According to the Examiner, the specification must be amended to remove the definition that is contradictory to the art and to the scope intended by Applicants. Applicants traverse these rejections.

Claim 2 is amended herein to remove the “\*”, rendering the rejection moot.

Claim 22 is canceled, and claims 23-24 are amended herein to clarify the scope of the instant claims, rendering the instant rejection moot.

In view of the above, Applicants respectfully submit that the rejections are overcome, and therefore the rejections may be withdrawn.

**Rejections Under 35 U.S.C. § 112, First Paragraph - Written Description**

Claims 1-17 and 31-37 remain rejected under 35 U.S.C. § 112, first paragraph as allegedly failing to meet the written description requirement. According to the Examiner, the limited disclosure of the structure and function of two examples of nitrilases in the claimed subgenus does not permit one of skill in the art to recognize members of the claimed subgenus of nitrilases. The Examiner also asserts that there is insufficient written description regarding the different method steps for making the compounds. Claims 22-24 and 38-43 are rejected under 35 U.S.C. § 112, first paragraph as allegedly containing new matter, thereby failing to meet the written description requirement. The Examiner alleges that there is no support for the limitation “enzymatically active fragment”. Applicants traverse these rejections.

As a preliminary matter, Applicants note that the Examiner asserts that the number of nitrilases known in the art at the time of filing is enormous compared to the subgenus of nitrilases useful in the claimed invention has no scientific basis. To Applicants knowledge, less than 20 nitrilases were identified in the art prior to the work of the inventors. If the Examiner has personal knowledge contrary to this, Applicants respectfully request that the source of this information be made of record.

While Applicants believe that the specification provides adequate written description for the class of nitrilases useful in the claimed methods, the claims as amended herein are limited to the two novel nitrilases disclosed in the application to expedite to prosecution. As the specification provides both the amino acid and nucleic acid sequences for the claimed nitrilases, the specification reasonably enables the claimed methods.

Applicants respectfully submit that the limitation “enzymatically active fragment” is fully supported by the specification as originally filed and therefore does not constitute new matter. *See* MPEP § 2163 (I) (B) (“While there is no *in haec verba* requirement, newly added claim limitations must be supported in the specification through express, implicit, or inherent

disclosure.”). The specification discloses compositions comprising enzymatically active fragments of the disclosed nitrilases. For example, the specification states at page 57, lines 26-28:

In some embodiments, the fragments, derivatives and analogs retain the same biological function or activity as the polypeptides of SEQ ID NOs: 2 and 4, and sequences substantially identical thereto. (emphasis added)

It is clear from this above disclosure that the fragments are enzymatically active fragments as they retain the same biological activity as the enzymes of SEQ ID NOs: 2 and 4. In another example, the specification discloses assays for identifying enzymatically active fragments of SEQ ID NOs: 2 and 4. *See* the specification at page, 58, line 26 to page 59, line 7. These assays are useful in indicating that the “fragment ... retains the enzymatic activity of the polypeptides in SEQ ID NOs:2 and 4.” *See* the specification at page 58, lines 30-31. Moreover, Applicants have amended the claims at issue to further clarify the fragments are fragments that retain the activity of the disclosed enzymes. In view of this disclosure, Applicants submit that the specification describes enzymatically active fragments in a way that reasonably conveyed to the ordinary artisan that the inventors had possession of the fragments at the time of filing, and thus this limitation does not constitute new matter.

Applicants respectfully submit that the rejections are overcome, and therefore, the rejections may be withdrawn.

**Rejections Under 35 U.S.C. § 112, First Paragraph - Enablement**

Claims 5 and 7-10 remain rejected under 35 U.S.C. § 112, first paragraph as allegedly requiring undue experimentation in order to practice the claimed methods, and claim 24 is added to this rejection. According to the Examiner, the predictability of finding or engineering other nitrilases to produce specific  $\alpha$ -substituted amino acids is extremely low considering the state of the art and the instant disclosure. Claims 24 and 38-44 are rejected under 35 U.S.C. § 112, first paragraph as allegedly failing to provide reasonable enablement for methods using the polypeptides related to SEQ ID NOs:2 or 4 or their encoding DNA. The Examiner argues that the ordinary artisan would be required to make nitrilase polypeptides within the sequence identity and functional limitations, thus requiring undue experimentation. Specifically, the Examiner asserts that the

variation of the nitrilase is not enabled for use in producing enantiomerically pure D-phenylglycine. Applicants traverse these rejections.

Applicants respectfully submit that the specification fully enables the ordinary artisan to practice the claimed methods because any experimentation that is required to practice the claimed methods is routine. No experimentation whatsoever is required for the ordinary artisan to make and use the nitrilases polypeptides as set forth in SEQ ID NOs:2 and 4 in the claimed methods. All that is required is the routine production of a polypeptide according to the specific sequences disclosed. Moreover, the working example in the specification demonstrates that the recombinantly generated nitrilases of SEQ ID NOs:2 and 4 function in hydrolyzing the substrate as predicted. Finally, the claimed methods employing variants of SEQ ID NO:2 and 4 employ only those that retain the same biological activity as the encoded enzyme. As the methods of making conservative substitutions are routine and the testing of such variants for biological activity is routine in view of the specification's disclosure, the claimed methods are reasonably enabled for the practice of the invention by the ordinary artisan.

In view of the above, Applicants respectfully submit that the rejections are overcome, and therefore the rejections may be withdrawn.

**Rejection Under 35 U.S.C. § 102 (b)**

Claims 1-4, 6, 11-17, 31, and 33-36 remain rejected under 35 U.S.C. § 102 (b) as allegedly being anticipated by Wakamoto et al. as evidenced by Iyer et al. The Examiner asserts that Wakamoto teaches equivalent nitrilases since recombinant generation does not change the nature of the nitrilase whatsoever and Iyer teaches the Strecker reaction and all its variation that are inherent features of Wakamoto. Claim 32 also remains rejected under 35 U.S.C. § 102 (b) as allegedly anticipated by Wakamoto et al. Again, the Examiner asserts that the recombinantly generated polypeptides are identical to the naturally occurring bacterial polypeptides, and thus they are anticipated. Claims 32 and 37 remain rejected under 35 U.S.C. § 102 (b) as allegedly anticipated by Bhalla et al. The Examiner asserts that the recombinantly generated polypeptides are identical to the naturally occurring bacterial polypeptides, and thus they are anticipated.

Applicants respectfully submit that Wakamoto fails to anticipate the currently pending claims because Wakamoto lacks any teaching regarding the specific nitrilases encoded by the amino acid sequence of SEQ ID NO:2 or SEQ ID NO:4 or by the nucleic acid sequence of SEQ ID NO:1 or SEQ ID NO:3. Wakamoto contains no disclosure that expressly or inherently discloses these novel nitrilases. Iyer provides no additional evidence relating to these nitrilases.

Likewise, Bhalla contains no disclosure of the claimed nitrilases, and therefore fails to anticipate the claimed methods.

In view of the above, Applicants submit that the rejections are overcome, and therefore the rejections may be withdrawn.

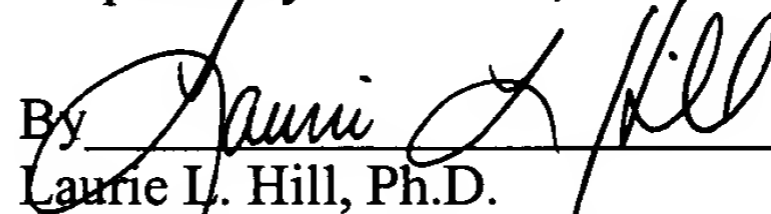
**CONCLUSION**

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 03-1952 referencing docket no. 564462006600. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: June 30, 2004

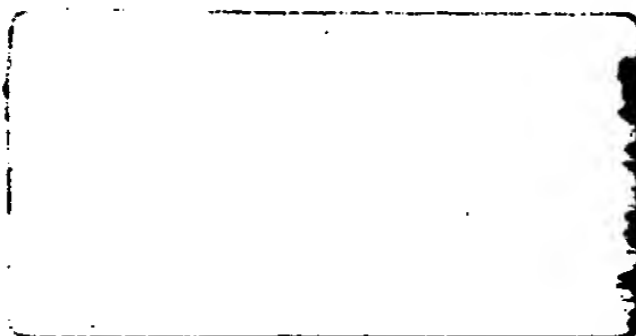
Respectfully submitted,

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Attorney's Docket No. 09010-113001	Express Mail Label No.	Mailing Date August 4, 2003	<b>For PTO Use Only</b> <i>Do Not Mark in This Area</i>
Application No. 09/751,299	Filing Date December 28, 2000	Attorney/Secretary Init GPE/sxs	
Title of the Invention <b>METHODS FOR PRODUCING ALPHA-SUBSTITUTED CARBOXYLIC ACIDS (AMENDED)</b>			
Applicant <b>Mark Madden et al.</b>			
Enclosures ·Information Disclosure Statement (2 pages) ·Form PTO-1449 (1 pages) ·Documents listed on the Form PTO-1449 (5 documents)			



**REMARKS**

The references cited on attached form PTO-1449 are being called to the attention of the Examiner. Copies of the references are enclosed. It is respectfully requested that the cited information be expressly considered during the prosecution of this application, and the references be made of record therein and appear among the "references cited" on any patent to issue therefrom.

The prior IDS and Form 1449 were submitted on September 6, 2001; July 17, 2002 and July 18, 2002, which was prior to the mailing of a first office action. It is now being resubmitted in connection with the office action mailed on April 17, 2003 to comply with 37 CFR 1.98(a)(2). Therefore, Applicant believes that no fee is required for submission of this statement. However, if a fee is required, the Commissioner is authorized to deduct such fee from the undersigned's Deposit Account No. 06-1050. If necessary, please deduct any necessary additional

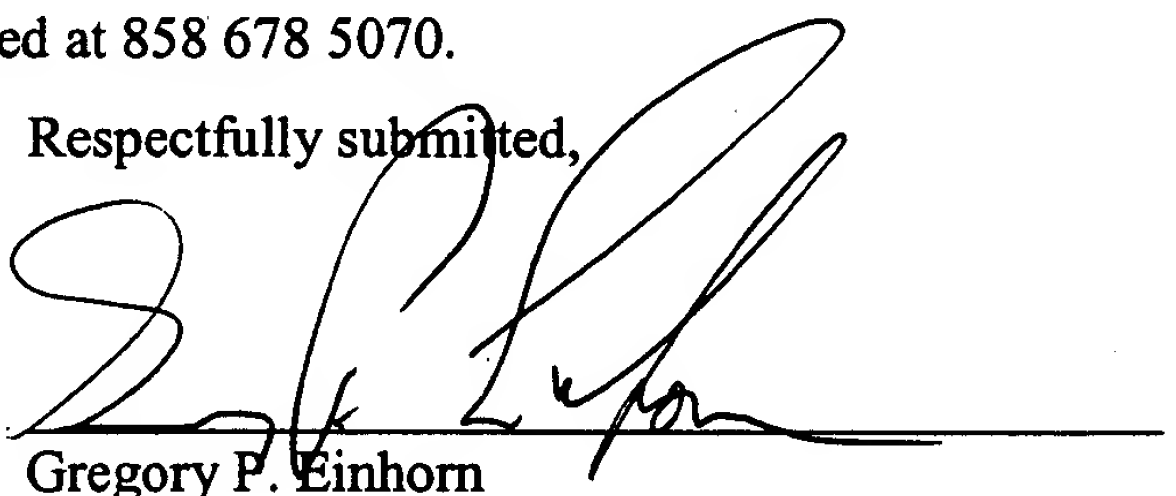
As provided for by 37 CFR 1.97(g) and (h), no inference should be made that the information and references cited are prior art merely because they are in this statement and no representation is being made that a search has been conducted or that this statement encompasses all the possible relevant information.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 858 678 5070.

Date: Aug 4, 2003

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Respectfully submitted,

  
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Mark Madden et al.                      Art Unit : 1652  
Serial No. : 09/751,299                                  Examiner : Unknown  
Filed : December 28, 2000  
Title : METHODS FOR PRODUCING ALPHA-SUBSTITUTED CARBOXYLIC  
ACIDS (AMENDED)

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

**SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT**  
**UNDER 37 CFR §1.97 and §1.98**

Sir:

Enclosed for filing in the above-referenced patent application is a Form PTO-1449, being submitted after a first Office action on the merits, but before receipt of a final Office action or a Notice of Allowance. The following documents related to this supplemental information disclosure statement are enclosed herewith:

- copy of Form PTO-1449
- copies of cited reference

Applicants respectfully request consideration of the remarks and references set forth herein.

CERTIFICATE OF MAILING BY FIRST CLASS MAIL

I hereby certify under 37 CFR §1.8(a) that this correspondence is being deposited with the United States Postal Service as first class mail with sufficient postage on the date indicated below and is addressed to the Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

AUGUST 4, 2003

Date of Deposit

Susan Sebovich

Signature

SUSAN SEBOVICH

Typed or Printed Name of Person Signing Certificate

Substitute Form PTO-1449 (Modified) 	U.S. Department of Commerce Patent and Trademark Office	Attorney's Docket No. 09010-113001	Application No. 09/751,299
		Applicant Mark Madden et al.	
		Filing Date December 28, 2000	Group Art Unit 1652

U.S. Patent Documents							
Examiner Initial	Desig. ID	Document Number	Publication Date	Patentee	Class	Subclass	Filing Date If Appropriate
	AA						
	AB						
	AC						
	AD						
	AE						
	AF						

Foreign Patent Documents or Published Foreign Patent Applications								
Examiner Initial	Desig. ID	Document Number	Publication Date	Country or Patent Office	Class	Subclass	Translation	
							Yes	No
	AG							
	AH							
	AI							
	AJ							
	AK							

Other Documents (include Author, Title, Date, and Place of Publication)		
Examiner Initial	Desig. ID	Document
	AL	Ogawa, et al., "Microbial enzymes: new industrial applications from traditional screening methods", <u>Trends in Biotechnology</u> , Vol. 17, No. 1, pp. 13-20 1999
	AM	Fournand, et al., "Monohydrozamic acid biosynthesis", <u>Journal of Molecular Catalysis B: Enzymatic</u> , Vol. 5, pp. 207-211, 1998
	AN	Nagasawa, et al., "Microbial transformations of nitriles", <u>TIBTECH</u> , Vol.7, pp 153-158, 1989
	AO	Kim, et al., "Cloning and expression of the nitrile hydratase and amidase genes from <i>Bacillus</i> sp. BR449 into <i>Escherichia coli</i> ", <u>Enzyme and Microbial Technology</u> , Vol. 27, pp. 492-501, 2000
	AP	Gabriel, et al., "High-performance liquid chromatographic study of the aromatic nitrile metabolism in soil bacteria", <u>Journal of Chromatography B</u> , Vol. 681, pp. 191-195, 1996

Examiner Signature	Date Considered
EXAMINER: Initials citation considered. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.	